"SYNTHESIS AND BIOLOGICAL EVALUATION OF THE BIOACTIVE NATURAL PRODUCTS"

FINAL- SYNOPSIS

OF THE Ph.D. THESIS TO BE SUBMITTED

TO

THE FACULTY OF SCIENCE AND TECHNOLOGY OF

MANGALORE UNIVERSITY

FOR AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

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JUNE 2023

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Date of registration : **01-03-2017**

Register No. :**MU/EXB/Ph.D./CR.206/Chem./2018-19/E.13**
Dated 26-02-2019

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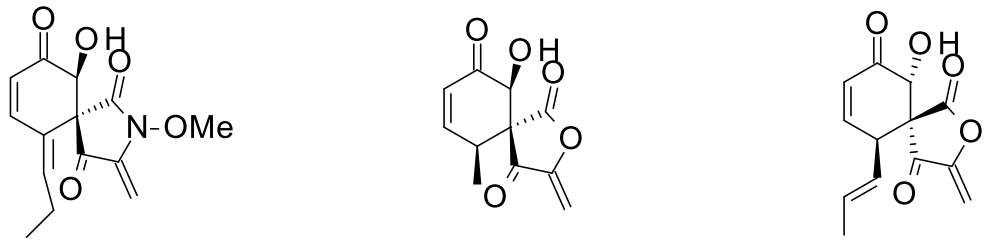
Introduction

Natural products are an important class of compounds used in both the pharmaceutical and crop protection industries.[1] The structural diversity and distinctive biological activity hold natural products at the center of drug discovery.[2] Natural compounds have long been employed for medicinal or agrochemical use, either directly or as derivatives. For instance, pyrethrin,[3] a natural substance, has been used as an insecticide directly and also as a derivative cypermethrin,[4] and emamectin, a derivative of abamectin,[5] has also been employed as an insecticide. The discovery of azoxystrobin,[6] a systemic fungicide frequently used in agriculture was made possible by the discovery of the natural product strobilurin A.[7]
Several naturally occurring spirocyclic compounds are known and represent as privileged structures in both pesticide and pharmaceutical because of their unique arrangement where two rings are connected by single atom.[8] The bioactivity of spirocyclic compounds is superior than the flat aromatic compounds due to their conformational flexibility as they can be easily fit into the biological target.[9] Synthesis of spirocyclic compounds has been attractive to the organic chemist owing to their applications in pharmaceutical, agrochemical[10] and asymmetric catalysis.[11] There are many bioactive natural products which contain a spirocyclic motif with antifungal and herbicidal activity.[12]
In 1988, Sugawara *et al.* isolated structurally novel spiro cyclic γ-lactams from cultures of the plant pathogenic fungus *Drechslera tritici-repentis* such as Triticones and related natural products.[13] Triticone A shows non selective herbicidal activity. Similarly, Mycosporulone[14] has antibacterial, antifungal activity and Arthropsolide C[15] exhibits antifungal activity.



1 Triticone A

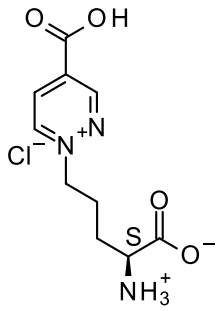
2 Mycosporulone

3 Arthropsolide C

Figure 1: Structures of Triticone A (**1**), Mycosporulone (**2**) and Arthropsolide C (**3**)

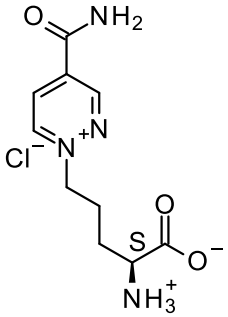
We were interested to explore the potential of these natural compounds with spirocyclic motifs as crop protection products.

Natural products have a long history of serving as inspirations for the design of novel compounds as crop protection products. Only 2% of the natural products are used directly as crop protection products and the majority of these are modified by varying the physicochemical properties to meet the requirements of the product.



Pyridazocidin (a)

4



Pyridazomycin (b)

5

Figure 2: Structures of Pyridazocidin (**4)**, Pyridazomycin (**5)**

We could come across several of these natural products having weak biological activity, later modified to develop a compound with commercial applications.

Pyridazocidin **4**, (Figure 2) a new antifungal antibiotic produced by *Streptomyces violaceoniger sp*. Griseofuscus was reported in 1997 by Gerwich. The natural product Pyridazocidin **4** was known to have weak herbicidal activity.[16] Our goal was to explore and modify few of these natural products with weak biological activity by varying its physicochemical properties to improve further its efficacy.

The thesis entitled "**Synthesis and Biological Evaluation of the Bioactive Natural Products**" has been divided into two parts,

Part A includes synthesize and biological activity of the (E/Z) *des*-hydroxy Triticone A and B related natural products. It has been also envisioned to develop suitable methodology for the spiro cyclisation for their synthesis.

Part B deals with the synthesis and biological activity of simplified analogues of Pyridazocidin **4.**

Part A: Synthesis and biological activity of (E/Z) *des*-hydroxy Triticone A and B related natural products

Part A has been divided into following four chapters

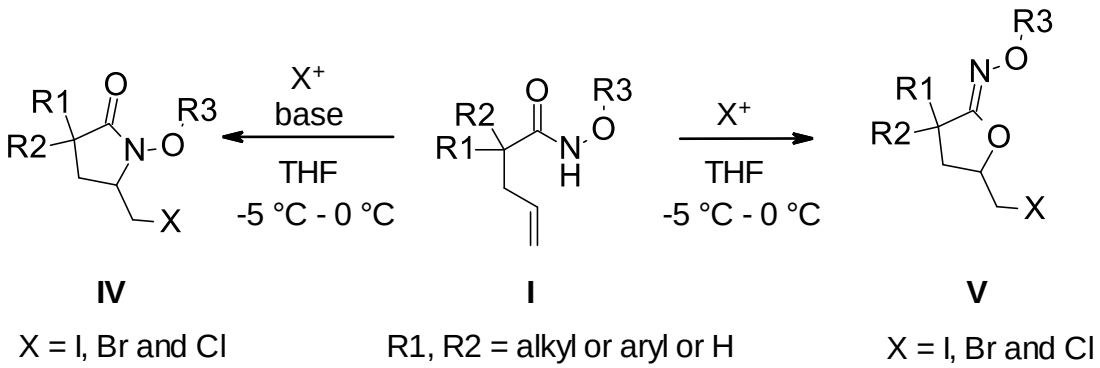
Chapter 1: Introduction

This is the introductory chapter deals with the importance of the spirocyclic natural products in the agrochemical industries. The synthetic reports on the spirocyclic natural products as Triticone A, Mycosporulone and Arthropsolide C with their physical properties and biological activity in publications appearing up to the year 2022 has been reviewed.

Similarly, importance of the quaternary nitrogen salts in crop protection research has been illustrated. The necessity of Pyridazocidin inspired bioactive compounds for weed spectrum has been discussed.

Chapter 2: Halocyclization of *N*-alkoxy Amides: Synthesis of *N*-alkoxy Lactams and Oximinolactones

This chapter describes the development of a simple and easy protocol to synthesize *N*-alkoxy lactams and lactones from γ,δ-unsaturated *N*-alkoxy amides. An intensive literature review on the synthesis of **γ**-lactams has been highlighted. Synthesis of amides from the corresponding ester or acid *via* allylation and then hydrolysis followed by amidation with different alkoxy group has been discussed.[17] The reaction optimization using the different base and solvent screening along with substrate scope for the **γ**-lactams and iminolactone has been illustrated.



Scheme 1: Synthesis of **γ**-lactams and iminolactone

We have developed the base mediated aminohalogenation reaction of the *N*-alkoxy amides using (LiHMDS or *n*BuLi, in THF at -5 °C using I_2 or NBS or NCS) and lactams were easily prepared from corresponding *N*-alkoxy amides. In most of the cases we obtained more than 85% selectivity towards the **γ**-lactams *Vs* iminolactone with optimized condition. The disubstituted amides gave well to excellent yield in haloamination reaction. NBS furnished the **γ**-lactam with excellent yield. (Figure 3).

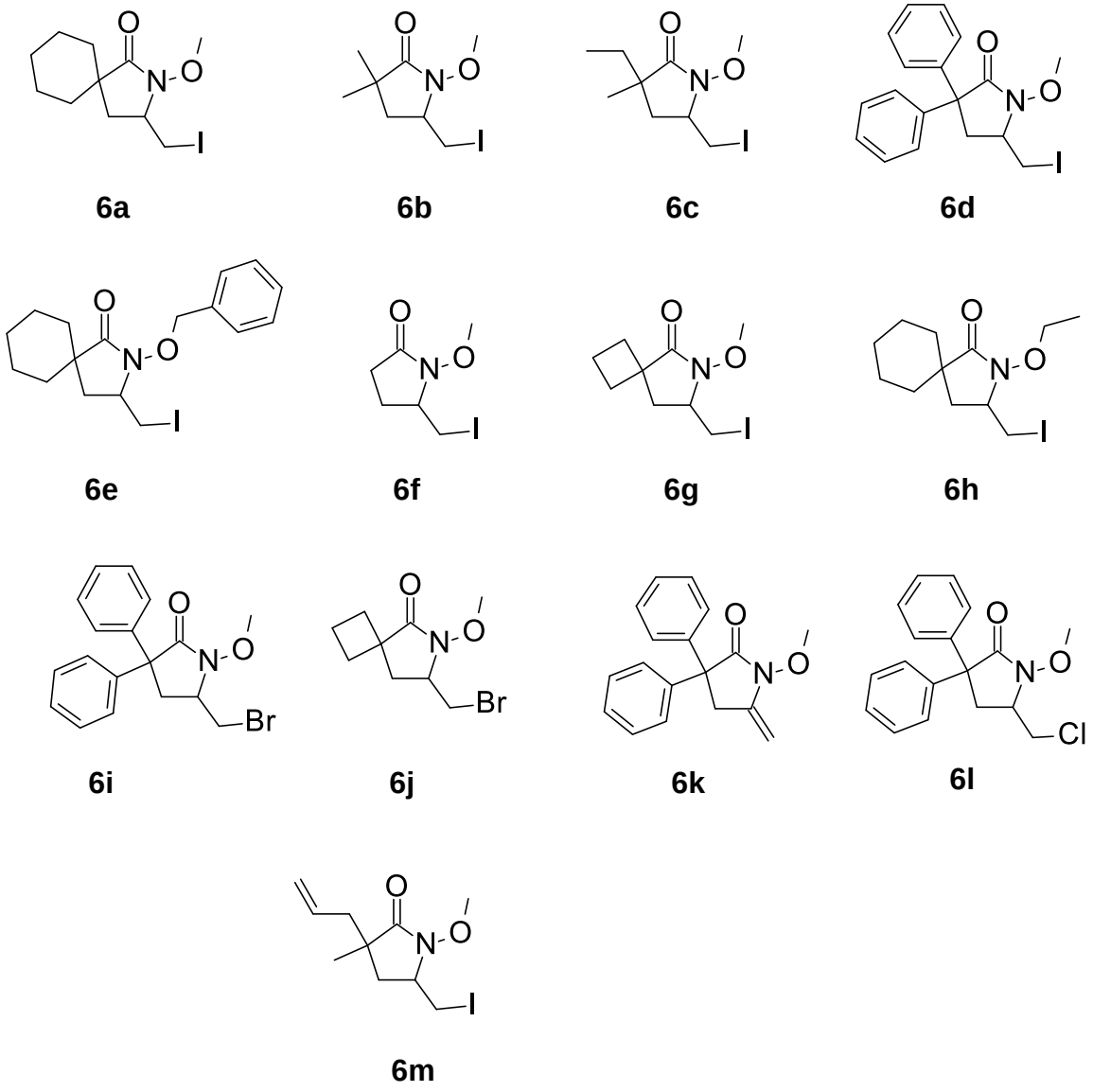


Figure 3. Examples of synthesized *N*-alkoxy lactams

Similarly, synthesis of iminolactone using weak base ($NaHCO_3$ or K_2CO_3) or without base is highly chemo selective and we have successfully synthesized different iminolactones shown below. (Figure 4)

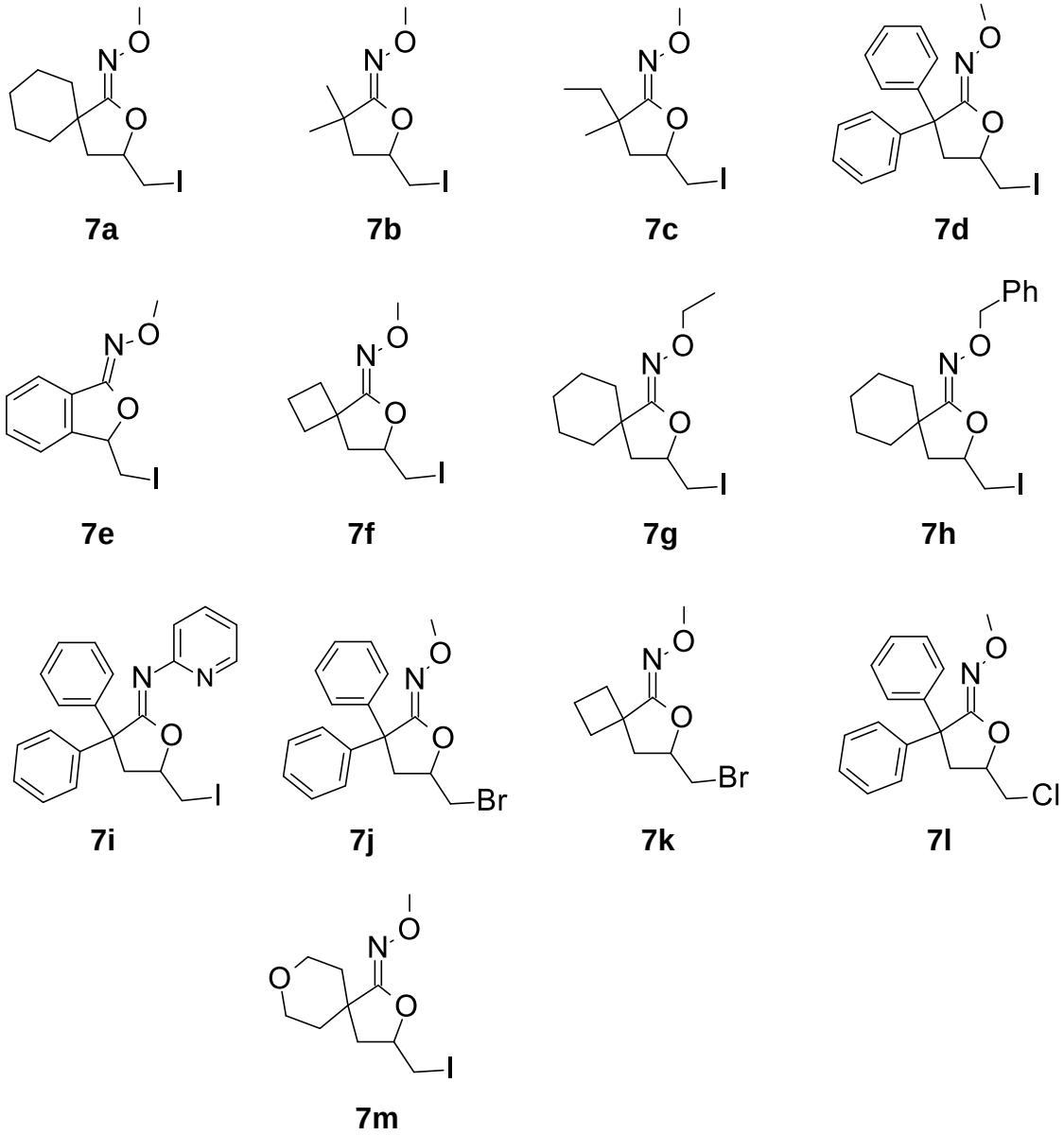


Figure 4. Examples of synthesized *N*-alkoxy iminolactone

Chapter 3: Total Synthesis of (E/Z) *des*-Hydroxy Triticone A and B using Aminohalogenation Methodology

This chapter describes the synthesis of (E/Z*) des*-hydroxy Triticone A and B natural product using our established methodology.

In 1988, Sugawara *et al.* isolated structurally novel spirocyclic γ-lactams from cultures of the plant pathogenic fungus *Drechslera tritici-repentis* (Figure 5).[18]

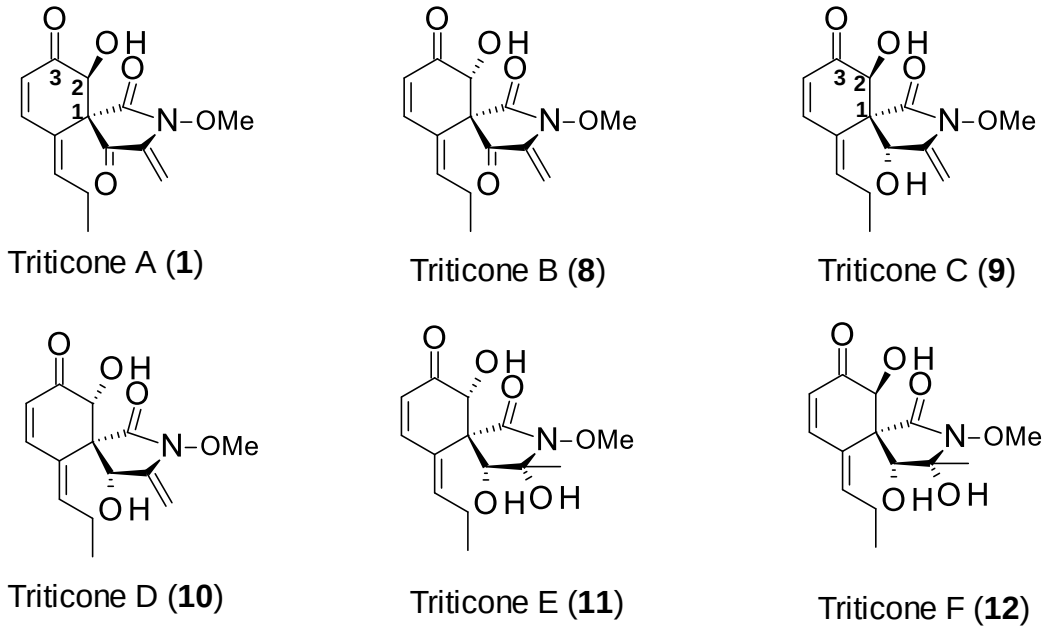


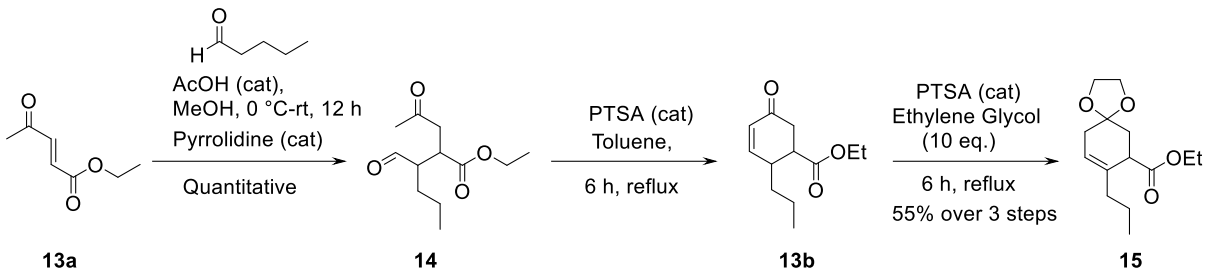
Figure 5. Triticone Family

These were called triticones A, B, C, D, E, and F depending on the minor structural variations in stereochemistry and oxidation states. Our interest in the triticone family emanated as potential herbicidal leads from the peculiar biological activity displayed by different members, wherein triticones A and B showed the highest phytotoxic activity in leaf protoplasts, while other members showed weaker or no phytotoxicity.[19]

This display promised interesting structure-activity relationships as well as potential to simplify the structural motif as a weed control lead. With this aim, we set out to gain synthetic access to the spirocyclic core of triticone family as, to the best of our knowledge, there is no synthetic report on triticones till date.

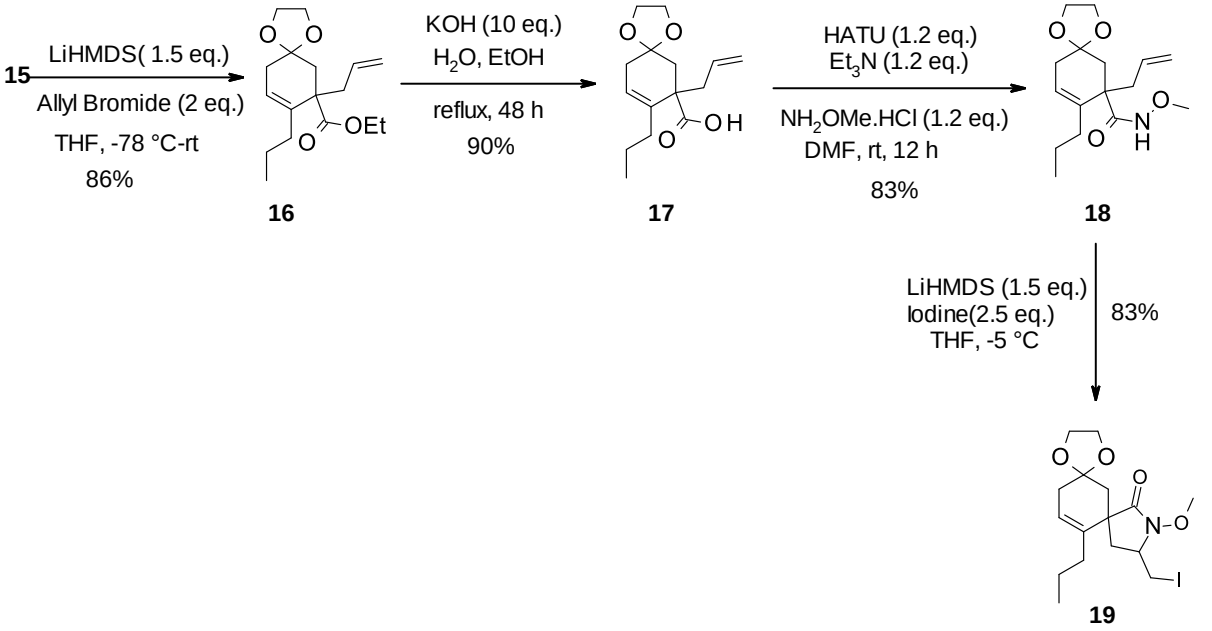
We started our endeavour *via* organocatalysed Michael addition of valeraldehyde (Scheme 2) on enone **13a**[20] to obtain γ-ketoester **14** in quantitative yield. Treatment of **14** with catalytic amount of PTSA resulted in the formation of α,β-unsaturated cyclohexenone **13b** which was protected with ethylene glycol to obtain cyclic ketal **15**.[21]

It is to be noted that during the ketal protection the double bond isomerisation occurs in the ring.



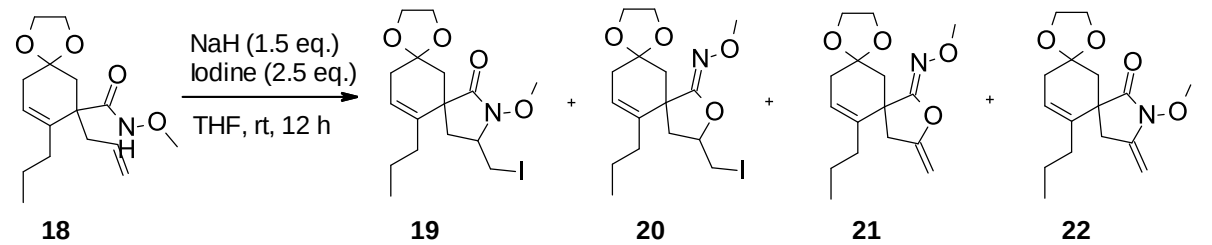
Scheme 2: Construction of cyclohexene cyclic ketal **15**

Ester **15** was then subjected to α-allylation using LiHMDS[22] to obtain the allylated intermediate **16** (Scheme 3). Saponification of ester **16** followed by acid-amine coupling of acid **17** with *O*-methyl hydroxylamine hydrochloride produced amide **18** in excellent yields.[23] Amide **18** was successfully converted into the desired iodolactam **19** using our established methodology.



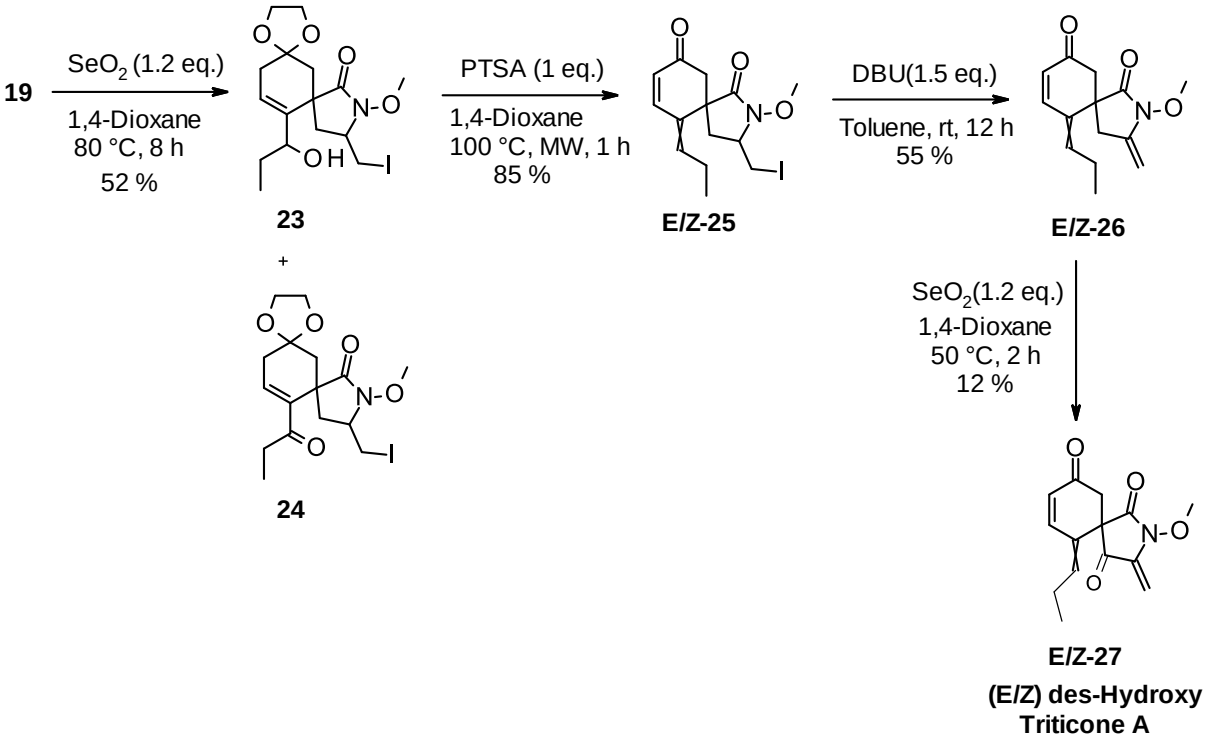
Scheme 3: Synthesis of iodolactam **19**

During the reaction optimization we have also isolated compounds **20, 21, 22** mentioned below (scheme 4).



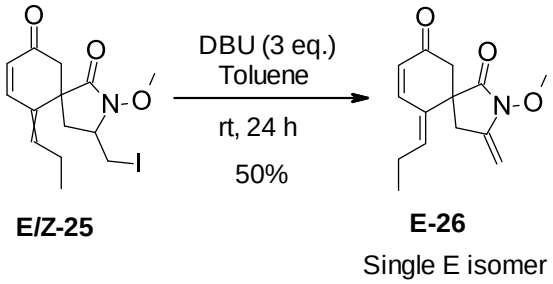
Scheme 4: Reaction optimization for iodolactamization **19**

To construct *exo* double bond in (E/Z)-**25** we used allylic oxidation followed by dehydration strategy (Scheme 5). The lactam **19** was subjected of oxidation in presence of SeO_2 to get allylic alcohol **23** along with corresponding over-oxidized ketone **24**, which was confirmed by X-ray crystal structure. Ketal deprotection using PTSA in 1,4-Dioxane gave dehydration as well as ring double bond isomerization to yield a 1:1 mixture of (E/Z)-**25**[24]



Scheme 5: Synthesis of (E/Z) *des*-hydroxy Triticone A

Compound (E/Z)-**25** (Scheme 5) were subjected to dehydroiodination to install the *exo* methylene group (E/Z)-**26** in presence of DBU.[25] Interestingly we have observed that treatment of (E/Z)-**25** with excess DBU and extended reaction time resulted in a single diastereoisomer of (E)-**26** (Scheme 6).



Scheme 6: DBU mediated double bond isomerization

The double bond isomerization can be explained based on Baylis–Hillman type addition of DBU (Scheme 6).[26] The dehydroiodination could be imagined to furnish the compound (E/Z)-**26,** which upon Michael addition of DBU at *δ*-position and subsequent selective elimination could yield more stable *E*-isomer**.**

With the key intermediate (E/Z)-**26** in hand, we embarked on the final double oxidation step to obtain the Triticone molecules. However, numerous oxidative conditions attempted on (E/Z)-**26** did not yield the desired double oxidation. The best result we could obtain was using selenium dioxide mediated allylic oxidation to obtain mono-hydroxylated compound, the *des*-hydroxy triticone (E/Z)-**27** (Scheme 5) in 12% isolated yield.

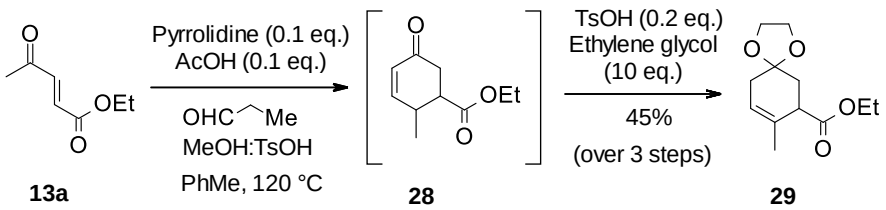
Chapter 4: Towards the total synthesis of Triticone related natural products: (±) Mycosporulone and (±) Arthropsolide

This section deals with the synthesis of Triticone related natural products using our strategy.

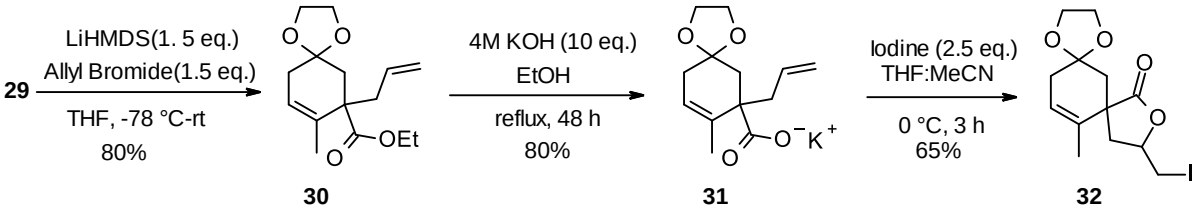
A novel fungal metabolite named Mycosporulone (Figure 1) was isolated by Mourad Kaouadji in 1993.[27] Wenge Cui *et al*. has synthesized the demethyl Mycosporulone and its C-6 epimer.[28] Michael E. Jung and Jonah J. Chang reported the first total synthesis of Mycosporulone and proposed the revised structure. The Mycosporulone showed antifungal and antibacterial activity. [29]

Our aim was to synthesize the advance intermediates of such natural products and investigate their biological activities in agrochemical industry.

The synthesis was initiated *via* organocatalysed Michael addition of propanal on enone **13a**[30] (Scheme 7) followed by treatment with catalytic amount of PTSA resulted in the formation of α,β-unsaturated cyclohexenone **28** which was protected with ethylene glycol to obtain cyclic ketal **29**.



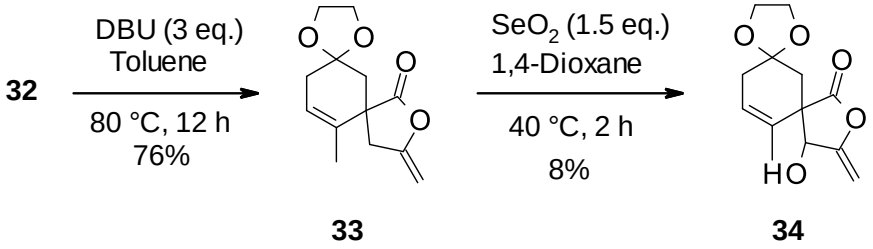
Scheme 7: Synthesis of cyclic ketal **29.**



Scheme 8: Synthesis of iodolactone **32**

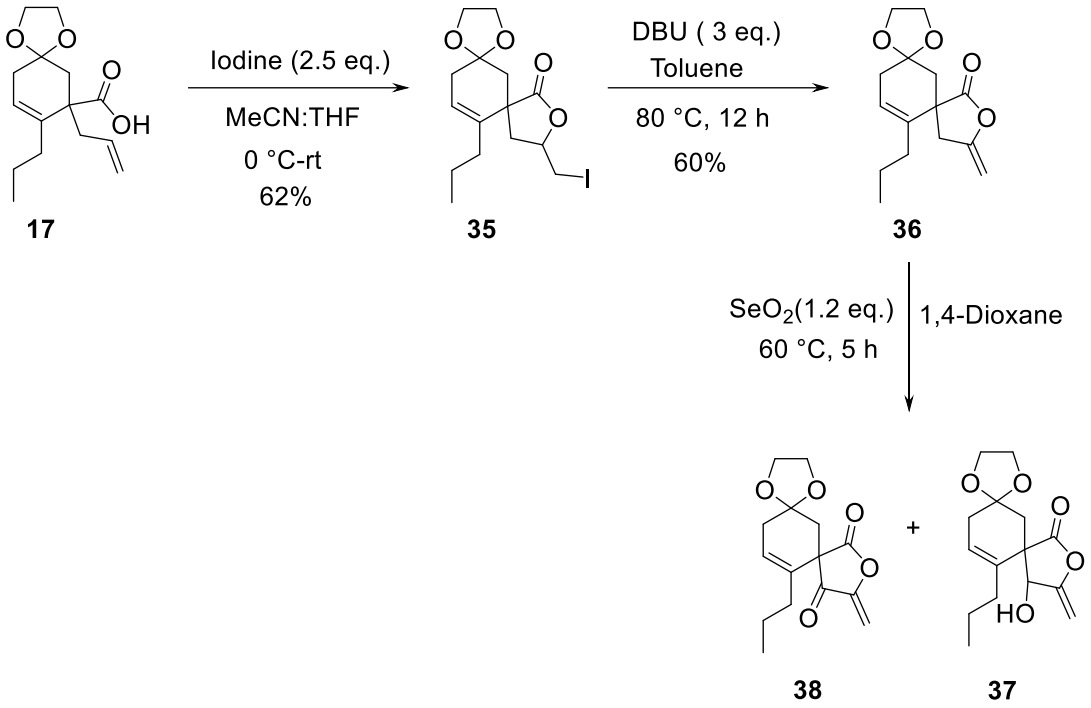
Ester **29** (Scheme 8) was then subjected to α-allylation using LiHMDS to obtain the allylated intermediate **30**. Saponification of ester **30** followed by iodolactonization furnished compound **32** with 65% isolated yield.[31]

The iodolactone **32** was further treated with DBU (Scheme 9) in toluene for dehydroiodination to yield compound **33** with exocyclic double bond.[32] The allylic oxidized intermediate **34** was achieved *via* oxidation using the selenium dioxide in 1,4-Dioxane.[33] Due to the formation of additional byproducts, the reaction yield was not very promising and could not be isolated in pure form.



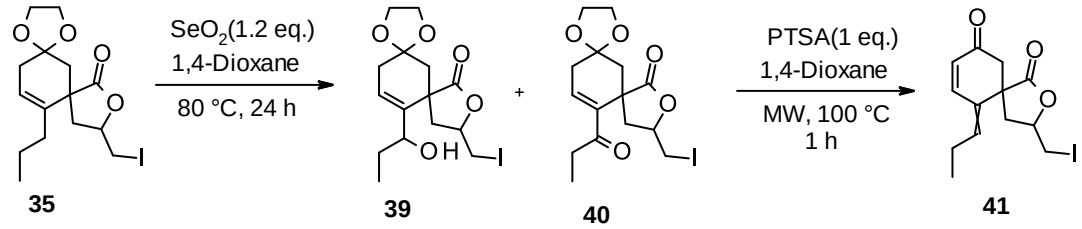
Scheme 9: Synthesis of allylic oxidized analogue **34**

Similarly, we applied this synthetic approach for Arthropsolide natural product.[34]



Scheme 10: Synthesis of allylic oxidized analogues **37**

The compound **17** (Scheme 10) was synthesized using the similar approach from compound **13a** from valeraldehyde (Scheme 3). Iodolactonization using iodine furnished compound **35** with 60% isolated yield**.** The dehydroiodination using DBU provided exocyclic double bond compound **36**. The allylic oxidiation using selenium dioxide in 1,4-Dioxane yield compound **37** with traces amount of the corresponding ketone **38**. It has been observed that these intermediates are very sensitive in case of stability and react with nucleophiles quickly.



Scheme 11: Synthesis of enone **41**

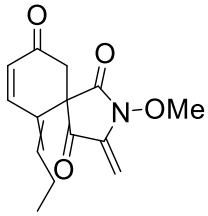
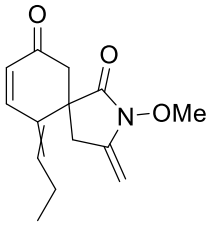
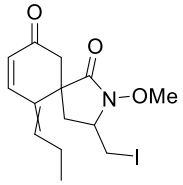
The allylic oxidation of iodolactone **35** (Scheme 11) furnished inseparable mixture of allylic alcohol **39** and corresponding ketone **40.** The mixture was subjected for the deprotection using PTSA and 1,4-Dioxane in MW condition isolated enone **41** along with unreacted ketone **40**.

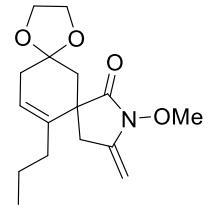
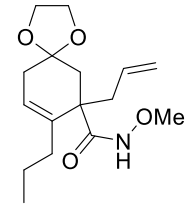
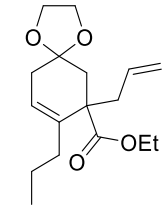
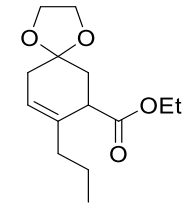
Biological activity of (E/Z) *des*-hydroxy Triticone A and B related natural products

The synthesized novel intermediates were investigated under biological discovery screening for fungicidal, insecticidal, herbicidal activities.

Fungicidal activity of several Triticone analogues are listed below:

Table 1: Fungicidal discovery screening

Substance	Rates g/ha	FDES				
		Pythium ultimum	*Phytophthora capsica*	*Botrytis cinerea*	*Gibberella Zeae*	*Septoria tritici*
		eff (%ASS)	eff (%ASS)	eff (%ASS)	eff (%ASS)	eff (%ASS)
	100	-	-	-	-	-
	20	100	100	100	100	100
	100	0	0	0	0	0
	20	0	0	0	0	0
	100	0	0	0	0	0
	20	0	0	0	0	0

	**100**	**0**	**0**	**0**	**0**	**0**
	20	**0**	**0**	**70**	**0**	**50**
	**100**	**0**	**0**	**0**	**0**	**0**
	20	**0**	**0**	**0**	**0**	**50**
	**100**	**0**	**0**	**0**	**0**	**0**
	20	**0**	**0**	**0**	**0**	**55**
	**100**	**0**	**0**	**0**	**0**	**0**
	20	**0**	**0**	**0**	**0**	**51**

Part B-Synthesis and biological activity of simplified analogues of Pyridazocidin

Chapter 5: Synthesis of simplified analogues of Pyridazocidin

This chapter deals with the synthesis of simplified analogues of Pyridazocidin **4** (Figure 6). The Pyridazocidin **4** (Figure 6) shows the weak herbicidal activity.[35] We wanted to explore further this motif by designing simplified analogues by replacing the pyridazine ring with pyridine and varying the acid functional group with different fused heterocycle with the desired physicochemical properties to exploit them as crop protection compounds. (Figure 6)

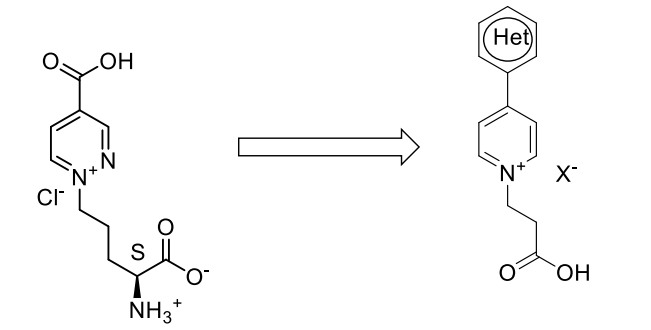


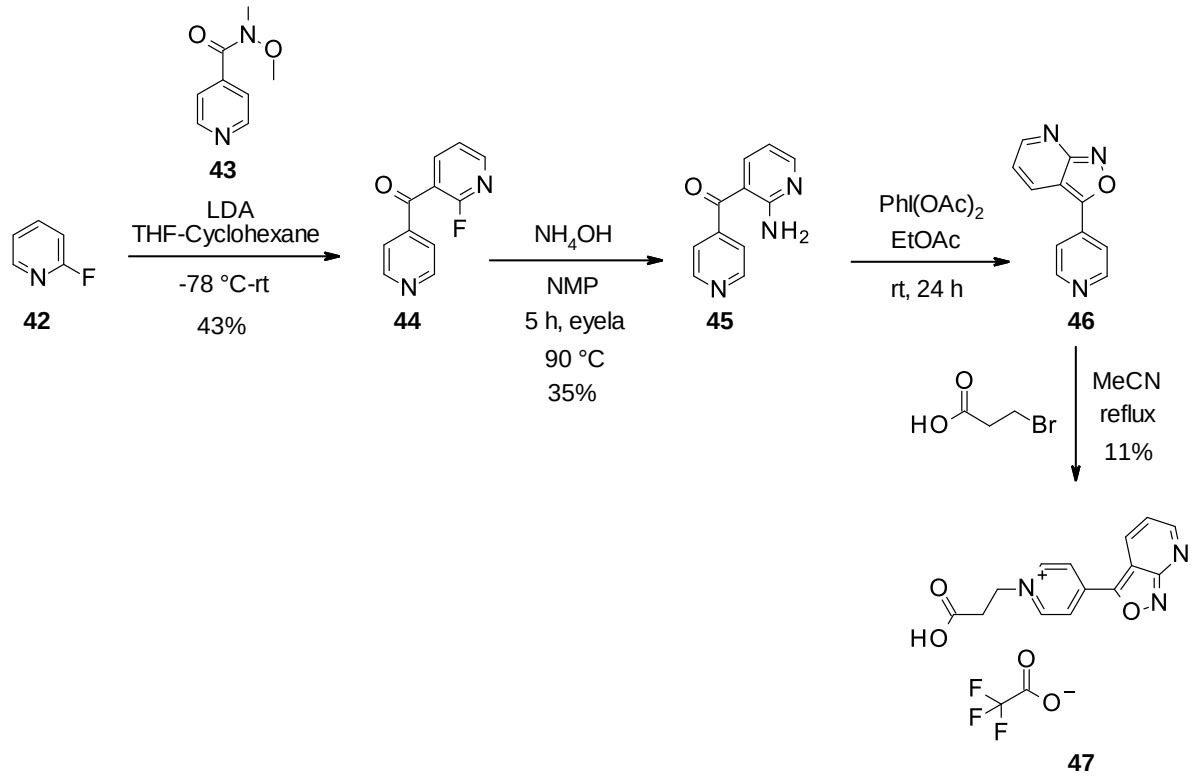
Figure 6: Synthesis of simplified analogues of Pyridazocidin **4**

We have synthesized different 6,5 fused heterocycles *via* Suzuki coupling of 4-pyridyl boronic acid with different heteroaryl halides. Alkylation of the pyridine derivatives using 3 bromo propionic acid or *tert* butyl bromo acetate in acetonitrile resulted in formation of quaternary pyridinium salts.

We have designed and synthesized 6 different compounds (**47**, **54**, **61**, **66**, **73** and **79**) and tested the herbicidal activity.

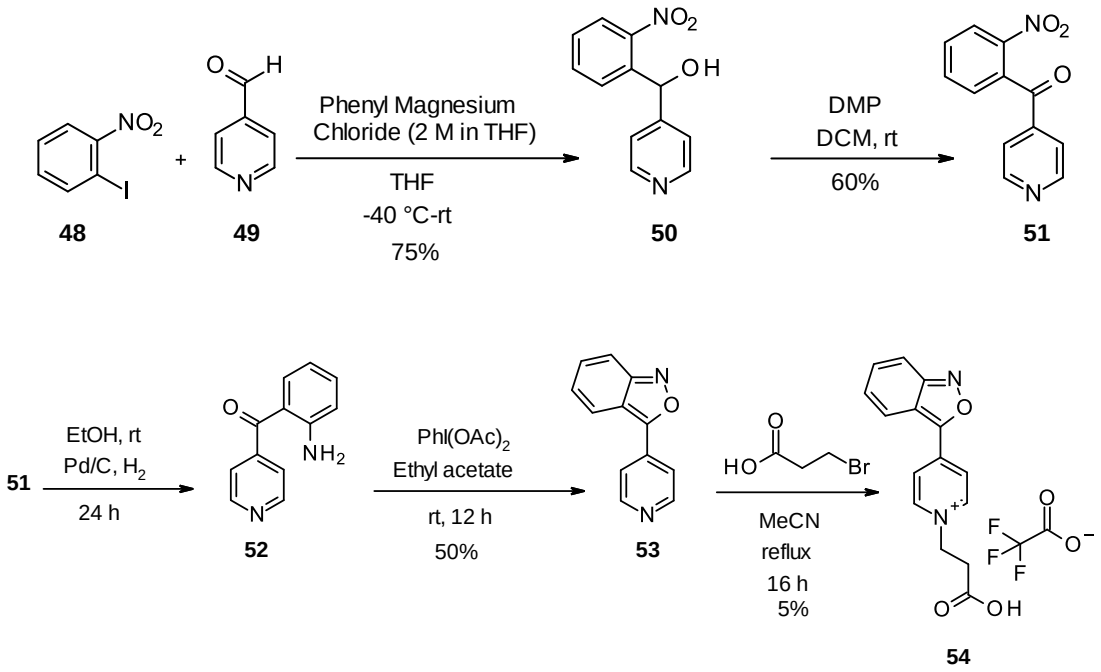
Synthesis of pyridinium salt **47** (Scheme 12) was initiated by treatment of 2-fluoro pyridine **42** with LDA to generate the carbanion ortho to fluorine followed by reaction with compound **43** [36] to obtain the compound **44** with 43% isolated yield.[37] Fluorine was substituted using the ammonium hydroxide in NMP at 90 °C afforded compound **45** with 35% yield. Heterocycle **46** was obtained *via* oxidative cyclisation by using PIDA in ethyl acetate at room

temperature. Synthesis of quaternary nitrogen salt using 3 bromo propionic acid in acetonitrile reflux condition achieved compound **47** with 11% isolated yield.



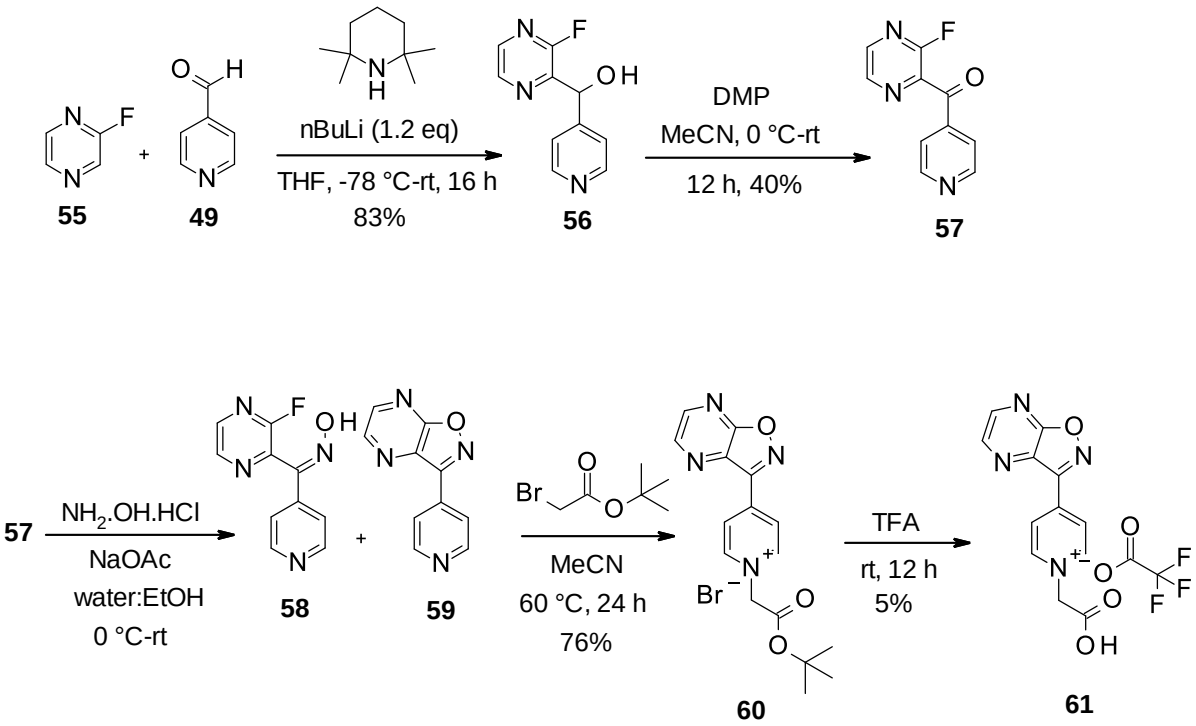
Scheme 12: Synthesis of 3-(4-isoxazolo[3,4-b]pyridin-3-ylpyridin-1-ium-1-yl)propanoic acid;2,2,2-trifluoroacetate

Compound **54** (Scheme 13) was synthesized by the treatment of compound **48** with phenyl magnesium chloride (2M solution in THF) at -40 °C to exchange Grignard followed by the addition of pyridine 4 carboxaldehyde, obtained alcohol derivative **50**.[38] Oxidation using Dess-Martin periodinane in DCM yield of ketone **51**. Nitro reduction was accomplished in palladium on carbon using hydrogen balloon to get amino ketone derivative **52** and used further without purification for oxidative cyclisation using PIDA at room temperature furnished compound **53.** The treatment of 3 bromo propionic acid with **53** in acetonitrile at refluxing condition achieved the desired compound **54.**



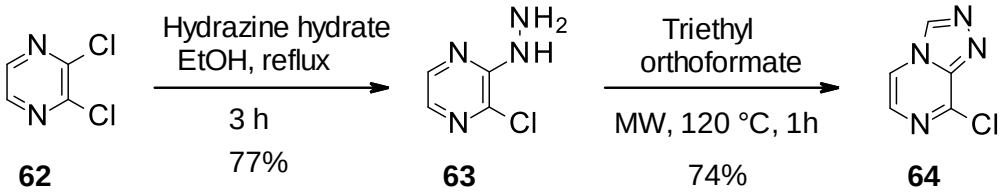
Scheme 13: Synthesis of 3-[4-(2,1-benzoxazol-3-yl)pyridin-1-ium-1-yl]propanoic acid;2,2,2-trifluoroacetate

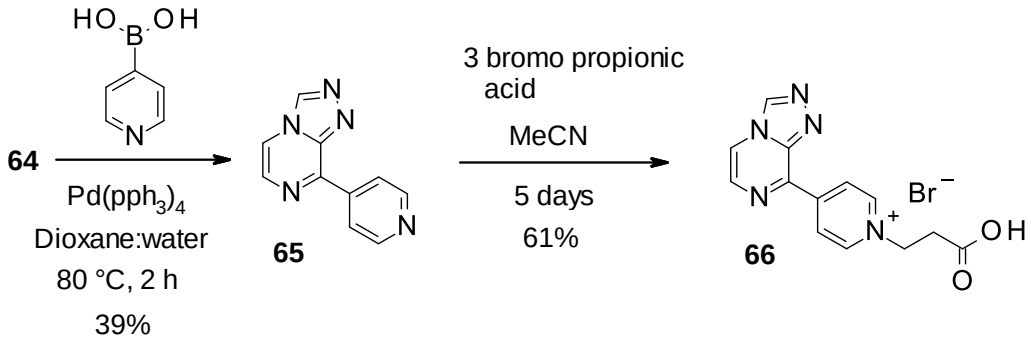
The treatment of 2-fluoro pyrazine **55** (Scheme 14) with LiTMP at -78 °C followed by the addition of pyridine carboxaldehyde obtained compound **56** with 83% isolated yield. The alcohol derivative **56** was oxidised to ketone **57** by using Dess-Martin periodinane and cyclised in presence of hydroxyl amine hydrochloride to generate desired heterocycle **59**. Reaction of *tert*-butyl bromo acetate with compound **59** in acetonitrile furnished compound **60** with 76% yield. Ester hydrolysis was carried out in TFA and afforded compound **61** after prep. Purification and structure was confirmed by using the 2D NMR spectroscopy.



Scheme 14: Synthesis of 2-(4-isoxazolo[4,5-b]pyrazin-3-ylpyridin-1-ium-1-yl)acetic acid;2,2,2-trifluoroacetate

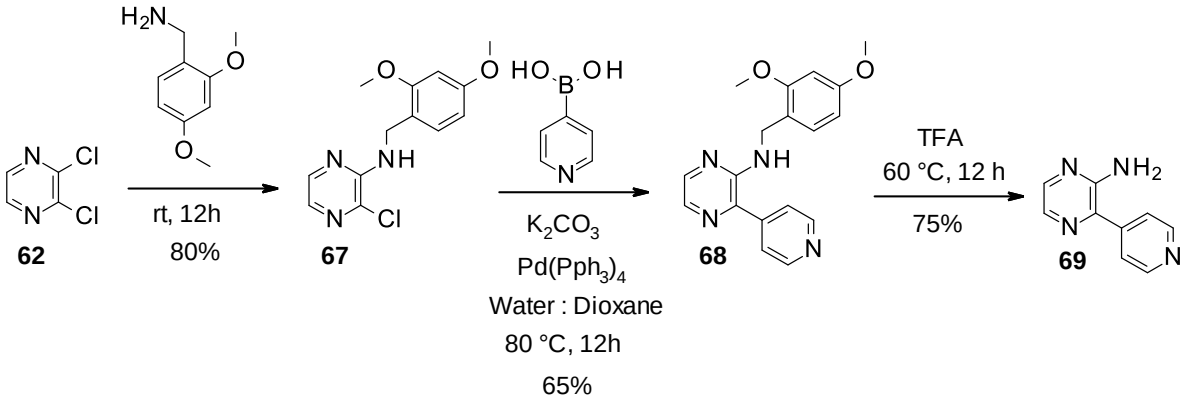
2,3 dichloro pyrazine **62** (Scheme 15) was treated with hydrazine monohydrate in ethanol with refluxing condition obtained hydrazine derivative **63** with 77% yield. The cyclisation using triethyl orthoformate in MW condition afforded compound **64**.[39] The Suzuki coupling of pyridine 4-boronic acid with compound **64** in presence of palladium tetrakis in 1,4-Dioxane-water mixture obtained compound **65.**[40] *N*-alkylation using 3 bromo propionic acid afforded compound **66.**

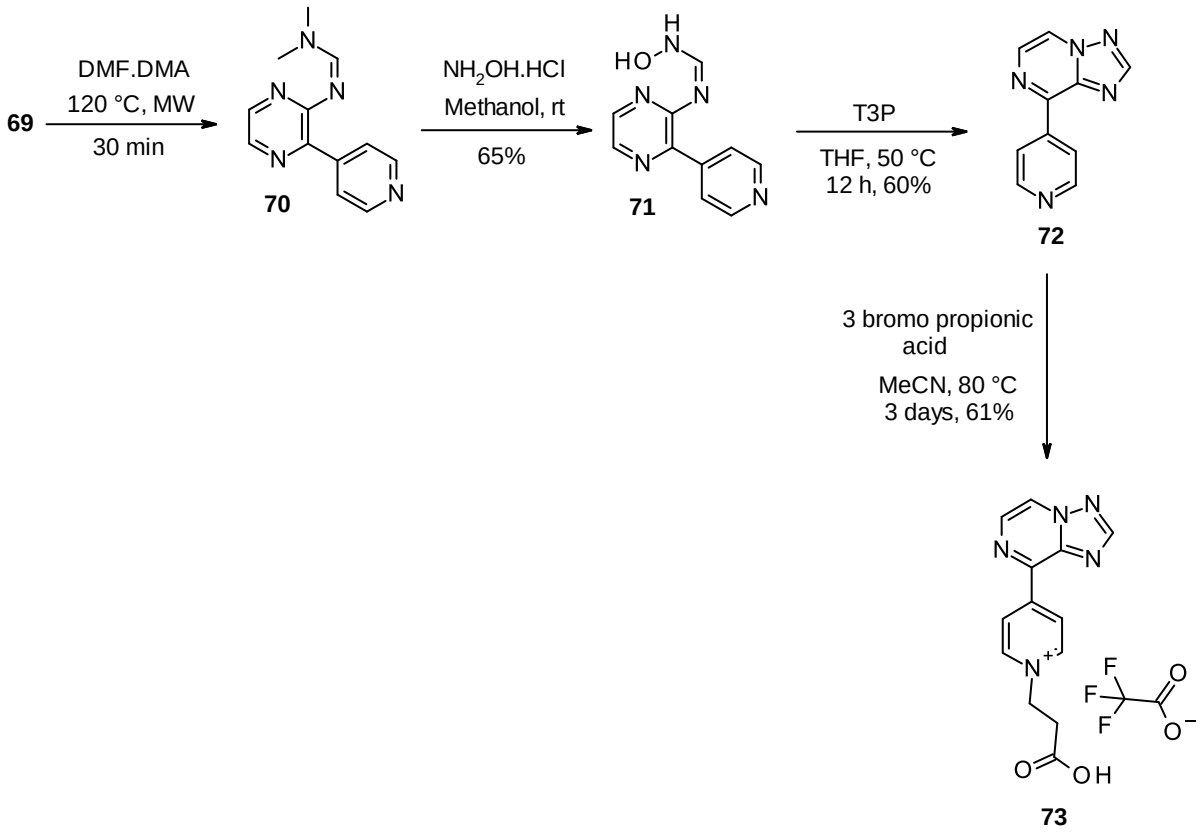




Scheme 15: Synthesis of 3-[4-([1,2,4]triazolo[4,3-a]pyrazin-8-yl)pyridin-1-ium-1-yl]propanoic acid;bromide

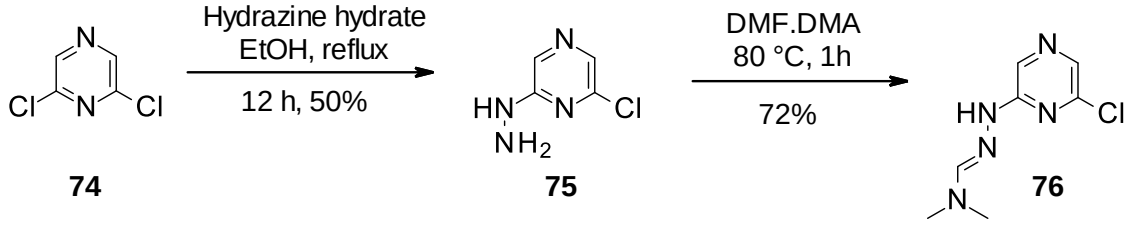
Similarly, compound **62** (Scheme 16) was treated with 2,4 dimethoxy benzyl amine at room temperature to obtain mono substituted compound **67** with 80% yield**.**[41] The Suzuki coupling with pyridine 4-boronic acid afforded compound **68** followed by deprotection by using TFA obtained pyrazine amine derivative **69.**[42] The enamine derivative **70** was isolated after the treatment with DMF.DMA which was further substituted using hydroxyl amine hydrochloride in methanol at room temperature to generate compound **71**.[43] The cyclisation using T3P in THF gave heterocycle **72**.[44] Finally, *N*-alkylated compound **73** was obtained with 61% yield.

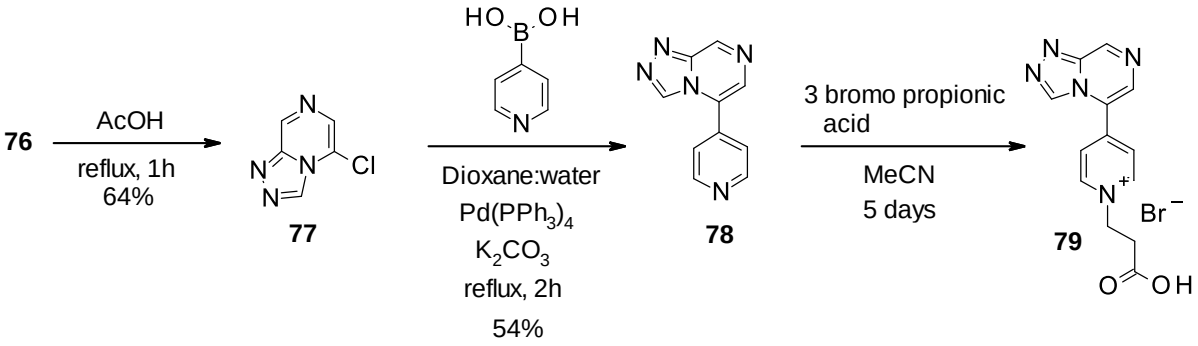




Scheme 16: Synthesis of 3-[4-([1,2,4]triazolo[1,5-a]pyrazin-8-yl)pyridin-1-ium-1-yl]propanoic acid;2,2,2-trifluoroacetate

2,6 dichloropyrazine **74** (Scheme 17) was treated with hydrazine monohydrate at refluxing condition obtained hydrazine derivative **75**.[45] Reaction with DMF.DMA ended with the adduct **76** only and there was no sign of the cyclized compound. The cyclisation was achieved when the adduct **76** was heated with acetic acid. Then Suzuki coupling with pyridine 4-boronic acid and *N*-alkylation using 3 bromo propionic acid obtained compound **79**.[46]

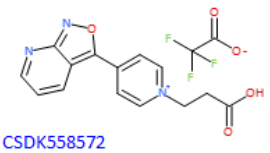
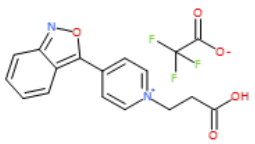
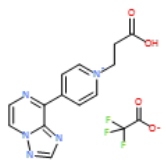




Scheme 17: Synthesis of 3-[4-([1,2,4]triazolo[4,3-a]pyrazin-5-yl)pyridin-1-ium-1-yl]propanoic acid; bromide

Biological Activity of Pyridazocidin related Compounds

This chapter describes the herbicidal activities of synthesized novel compounds. Herbicidal activity of some compounds tabulated below.

Substance (CSN)	Rates	HEPS														
		H-NSH-6-pr-so-E						H-NSH-6-po-so-E				H-NSH-5-po-so-E				
		AMAP	LOLPE	EPHHL	SETFA	ECHCG	IPOHE	AMAP	CHEAL	EPHHL	IPOHE	ELEIN	LOLPE	DIGSA	SETFA	ECHCG
		phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%	phy (%
		13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	500	0	0	0	0	0	0	90	90	20	50	70	20	90	80	60
	130	NC	0	0	0	0	0	90	70	40	20	10	10	NC	30	20
CSDK558572	60	0	0	0	0	0	0	90	30	20	10	20	10	60	60	20
	500	0	0	0	0	0	0	100	60	60	20	70	20	70	30	20
	130	0	0	0	0	0	0	90	50	20	10	80	10	50	20	10
CSDK558574	60	0	0	0	0	0	0	50	70	30	10	30	10	20	20	20
	500	0	0	0	0	0	0	0	0	30	0	30	10	30	30	20
	130	0	0	0	0	0	0	10	10	30	0	20	0	20	10	10
CSDL906718	60	0	0	0	0	0	0	0	0	10	0	10	0	10	10	10

Chapter 6: Summary & Conclusion

A summary of the whole study is made, and conclusions drawn based on the study are reported.

References:

1) Loiseleur, O. *Chimia*. **2017**, *71*, 810–822.

2) Hong, J. *Curr. Opin. Chem Biol.* **2011**, *15*, 350–354.

3) Shawkat, M.S.; Khazaal, Q, A.; Majeed, M. R.; *Iraqi J. Sci.* **2011**, *52*, 456–463.

4) Stephenson, R. R. *Aquat. Toxicol.***1982**, *2*,175–185

5) Yamashita, S.; Hayashi, D.; Nakano, A.; Hayashi, Y.; Hirama, M. *J. Antibiot*. **2016**, *69*, 31–50.

6) Liu,Y. G.; Luo, Y.; Lu, Y.; *J. Chem. Res*. **2015**, *39*, 586–589.

7) Anke, T.; Oberwinkler, F. *J. Antibiot*. **1977**, 806–810

8) Chupakhin, E.; Babich, O.; Prosekov, A.; Asyakina, L.; Krasavin, M.; Tormo, J.R.; *Molecules*. **2019**, *24*, 4165.

9) Zheng Y., Tice C.M., Singh S.B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682.

10) Smith L.K., Baxendale I.R. *Org. Biomol. Chem.* 2015, *13*, 9907–9933.

11) Franz, A. K.; Hanhan, N.V.; Ball J.N.R.; | *ACS Catal.* **2013**, *3*, 540−553.

12) Tsuji N., Kobayashi M., Wakisaka Y., Kawamura Y., Mayama M., Matsumoto K. *J. Antibiot.* **1976,** *29*, 7–9.

13) Sugawara, F.; Takahashi, N.; Strobel, G.A.; Strobel, S.A.; Lu, H. S. M.; Clardy, J.; *J. Am. Chem. SOC.* **1988**, *110*, 4086−4087.

14) Gusmao, N.B.D.; Steiman, R.; Murandi, F.S.; *J. Nat. Prod*. **1993**, *56*, 2189−2192

15) a) Ayer, W.A.; Craw, P.A.; Neary, J.; *Can. J. Chem.* **1992**, *70*, 1338−1347. b) Ayer, W.A.; Craw, P.A.; *Can. J. Chem.* **1992**, *70*, 1348−1355.

16) Gerwick, B. C.; Fields, S. S.; Graupner, P. R.; Gray, J. A.; Chapin, E. L.; Cleveland, J. A.; Heim, D. R.; *Weed, Sci.* **1997**, *45*, 654–657.

17) a) Shen, K.; Wang, K. *Chem. Sci.*, **2015**, *6*, 4279–4283. b) Shen, K.; Wang, Q.;

J. Am. Chem. Soc. **2017**, *37*, 13110–13116.

18) Sugawara, F.; Takahashi, N.; Strobel, G.A.; Strobel, S.A.; Lu, H. S.M.; Clardy, J.; *J. Am. Chem. Soc.* **1988**, *110*, 4086–4087.

19) Kenfield, D.; Strobel, S.; Sugawara, F.; Berglund, D.; Strobel, G. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 174–182.

20) Wang, J.; Ma, A.; Ma, D.; *Org. Lett*. **2008**, *10*, 5425–5428.

21) Jung, M. E.; Chang, J. J.; *Org. Lett*. **2012**, *14*, 4898–4901.

22) Nambu, H.; Hirota, W.; Fukumoto, M.; Tamura, T.; Yakura, T.; *Chem. Eur. J.* **2017**, *23*, 16799–16805.

23) Valeur, E.; Bradley, M.; *Chem. Soc. Rev.* **2009**, *38*, 606–631.

24) Kato, M.; Matsumura, Y.; Heima, K.; Fukamiya, N.; Kabuto, C.; Yoshikoshi, A.; *Tetrahedron.***1987**, *43*, 711–722.

25) Chen, L.; Kim, Y. M.; Kucera, D. J.; Harrison, K. E.; Bahmanyar, S.; Scott, J. M.; Yazbeck, D. *J. Org. Chem.* **2006**, *71*, 5468–5473.

26) Chittimalla, s. K.; Koodalingam, M.; Bandi, C.; Putturu, S.; Kuppusamy, R.: *RSC Adv.*, **2016**, *6*, 1460–1465.

27) Kaouadji, M.; Gusmao, N.B.D.; Steiman, R.; Murandi, F.S.; *J. Nat. Prod*. **1993**, *56*, 2189−2192.

28) Kraus, G. A.; Cui, W. *Synlett.* **2003**, *1*, 95–96.

29) Jung, M. E.; Chang, M. E. *Org. Lett.* **2012**, *14*, 4898–4901.

30) Wang, J.; Ma, A.; Ma, D.; *Org. Lett*. **2008**, *10*, 5425–5428.

31) a) Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K. *J. Am. Chem. Soc*. **2016**, *138*, 10597−10604. b) Ventre, S.; R. Petronijevic, F.; W. C. MacMillan, D. *J. Am. Chem. Soc.* **2015**, *137*, 5654−5657.

32) Chen, L.; Kim, Y. M.; Kucera, D. J.; Harrison, K.E.; Bahmanyar, S.; Scott, J.M.; Yazbeck, D.; *J. Org. Chem.* **2006**, *71*, 5468–5473.

33) Nakamura, A.; Nakada, M. *Synthesis*. **2013**, *45*, 1421–1451

34) a) Ayer, W.A.; Craw, P.A.; Neary, J.; *Can. J. Chem.* **1992**, *70*, 1338−1347. b) Ayer, W.A.; Craw, P.A.; *Can. J. Chem.* **1992**, *70*, 1348−1355

35) Gerwick, B. C.; Fields, S. S.; Graupner, P. R.; Gray, J. A.; Chapin, E. L.; Cleveland, J. A.; Heim, D. R.; *Weed, Sci.* **1997**, *45*, 654–657.

36) Kim, J. G.; Jang, D. O.; *Bull. Korean Chem. Soc*. **2010**, *31*, 171–173.

37) Han, F.; Lin, S.; Liu, P.; Liu, X.; Tao, J.; Deng, X.; Yi, C.; and Xu, H.; *ACS Med. Chem. Lett.* **2015**, *6*, 434–438.

38) Wanga, L.; Xieb, S.; Ma, L.; Chen, Y.; Lu, W.; *Bioorg. Med. Chem.***2015**, *23*, 1950–1962.

39) Zhang, B.; Liu, X.; Xiong, H.; Zhang, Q.; Sun, X.; Yang, Z.; Xu, S.; Zheng, P.; Zhu, W.; *New J. Chem.* **2020**, *44*, 9053.

40) Kumaravel, M.; Kumar, P.; Balakrishna, M.; *J Chem Sci.* **2014**, *126*, 711–716.

41) Du, X.; Gustin, D. J.; Chen, X.; Duquette, J.; McGee, L. R.; Wang, Z.; Ebsworth, K.; Henne, K.; Lemon, B.; Ma, J,; Miao, S.; Sabalan, E.; Sullivan, T. J.; Tonn, G.; Collins, T. L.; Medina, J. C.; *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5200–5204.

42) Jung, M. E.; Koch, P.; *Tetrahedron Lett.* **2011**, *52*, 6051–6054.

43) Komin, A. P.; Street, R. W.; Carmack, M.; *J. Org. Chem.*, **1975**, *40*, 2749–2752.

44) Ayothiraman, R.; Bandaru, D.; Paranthaman, R.; Fenster, M.; Eastgate, M. D.; Vaidyanathan, R.; *Org. Process Res. Dev.* **2019**, *23*, 2510−2515.

45) Korsik, M.; Tse, E. G.; Smith, D. G.; Lewis, W.; Rutledge, P. J.; Todd, M. H.; *J. Org. Chem.* **2020**, *85*, 13438–13452.

List of Publications/Patents:

A] In National/International Journals.

1. **Pyridinium compounds as herbicidal compounds and their preparation**

By: Scutt, James Nicholas; Willetts, Nigel James; **Chakave, Sunil**; Acharya, Vanitha; Phadte, Mangala; Sasmal, Swarnendu; Kandukuri, Sandeep Reddy; Tate, Joseph Andrew

World Intellectual Property Organization, WO2021058595 A1 2021-04-01.

2. **Pyridinium derivatives as herbicides and their preparation, agricultural compositions and use in the weed control** By: Scutt, James Nicholas; Willetts, Nigel James; Tate, Joseph Andrew; Croft, Rosemary Anna; McGranaghan, Andrea; **Chakave, Sunil**; Acharya, Vanitha; Phadte, Mangala.

   World Intellectual Property Organization, WO2021110890 A1 2021-06-10.

3. **Total Synthesis of (E/Z) *des*-Hydroxy Triticone A and B**

   By: **Sunil Dattatray Chakave**, Shrikant Shete, Sandeep Reddy Kandukuri, Mark Montgomery, Bhanu N. Manjunath and Ravindra Punjaji Sonawane. (https://doi.org/10.1002/ejoc.202201205).

4. **Base-Mediated Haloamination of the *N*-alkoxy amides: Synthesis of Lactams and Oximinolactones**

   By: **Sunil Dattatray Chakave**, Venunath Hapse, Anupa Dessai, Mark Montgomery, Ravindra Punjaji Sonawane, Sandeep Reddy Kandukuri, Bhanu N. Manjunath. (*Manuscript Communicated to JOC*).

B] In National/International Conference Proceedings

1. **Metal Free Aminoiodination/Oxyiodination of γ,δ-unsaturated *N*-Alkoxy Amides: Synthesis of Iminolactones and Lactams** by **Sunil Dattatray Chakave**, Anupa Dessai, Mark Montgomery, Ravindra Punjaji Sonawane, Sandeep Reddy Kandukuri, Bhanu N. Manjunath Presented in the 29th CRSI National Symposium in Chemistry held at IISER Mohali, during 6th to 9th July, 2022. **Abstr. No: PP -291**.

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